PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P2434PC00	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/NO2004/000202	International filing date *(day/month/year)* 02.07.2004	Priority date *(day/month/year)* 04.07.2003
International Patent Classification (IPC) or national classification and IPC A61K35/60		
Applicant THIA MEDICA AS et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (Indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the International application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.12.2004	29.07.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Hars, J Telephone No. +49 89 2399-7825

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NO2004/000202

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-24	as published
Claims, Numbers	
1-16	received on 31.01.2005 with letter of 27.01.2005
Drawings, Sheets	
1/4-4/4	as published

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-16
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Reference is made to the following documents:

D1: YAHIA D.A. ET AL.: 'Tissue antioxidant status differs in spontaneously hypertensive rats fed fish protein or casein' J. NUTR. vol. 133, 2003, pages 479 - 482, XP002903835

D2: SUGIYAMA K. ET AL.: 'Hypotensive effect of fish protein hydrolysate' NIPPON NOGEIKAGAKU KAISHI vol. 65, no. 1, 1991, pages 35 - 43, XP002903836

D3: US-A-4 294 856

The documents D6-D9 were not cited in the international search report. Copies of the documents are appended hereto.

D6: LIASET B. ET AL.: 'Studies on the nitrogen recovery in enzymic hydrolysis of Atlantic salmn (Salmon salar, L.) frames by ProtamexTM protease' PROCESS BIOCHEMISTRY vol. 37, pages 1263-1269, June 2002

D7: LIASET B. ET AL.: 'Chemical composition and theoretical nutrional evaluation of the produced fractions from enzymic hydrolysis of salmon frames with ProtamexTM' PROCESS BIOCHEMISTRY vol. 38 Nr 12, online publication in HTML format, available online 7 january 2003

D8: BERGERON N. ET AL.: 'Influence of fish protein as compared to casein and soy protein on serum and liver lipids and serum lipoprotein cholesterol levels in the rabbit' ATHEROSCLEROSIS, vol. 78, Nr 2-3, pages 113-122, 1989

D9: ZHANG X. ET AL.: 'Influence of dietary fish proteinson plasma and liver cholesterol concentrations in rats' BRITISH JOURNAL OF NUTRITION, vol. 69, Nr 3, pages 767-777, 1993

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 INVENTION

Fish protein hydrolysate is used to treat cardiovascular diseases. Claimed is the second medical and non-medical use (nutrional preparation) and a process of preparation.

V.2 CLARITY

Claims 1-3,7-11,16 all relate to a second use of fish protein hydrolysate (FPH) where the composition is either pharmaceutical or nutrional.

A nutrional composition that is for the "prevention" or "treatment" of fatty liver or other disorders is a non-medical use.

This authority has set clear lines relating to the novelty of a second medical and non-medical use.

In the case of a non-medical use where the intended use is claimed as like "for the use X", the intended use cannot confer novelty.

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1,D3 is not mentioned in the description, nor are these documents identified therein.

Although claims 1-3 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.

Claims 14 and 15 are entirely redundant over claim 4.

V.3 PRIOR ART

If not otherwise specified, subject matter of cited documents relates to the passages indicated in the search report.

D1

D1 discloses that rats which had been fed a fish protein diet (from SEAH International, Vimille (correct spelling: Wimille), France: 94% purity, almost lipid-free (0.05% fatty acids) had a lowered blood pressure and reduced plasma total cholesterol levels as compared to rats which had been fed a casein diet. Thus, fish protein enhances protection against cardiovascular diseases.

Note:

The skilled person reading D1 would have understood that a protein content of 94% and a fatty acid content of 0.05% can only be achieved with protein hydrolysates and not with whole protein.

This examining division therefore believes that the employed fish protein product in D1 was in fact a fish protein hydrolysate, and that this teaching was immediately accessible to the skilled person.

D2

D2 describes a fish protein hydrosylate (FPH) prepared from defatted sardine meal by treatment with alkaline protease (i.e. pH>7). When administered to spontaneously hypertensive rats (SHR), FPH reduced blood pressure and a diet containing FPH as the sole protein source had a stronger hypotensive effect and a higher survival ratio in stroke-prone SHR compared to a commercial diet.

As the document is in Japanese, no further process details are understood by this Examining division.

D3

D3 relates to a process for producing a milk replacer for raising infant pigs and other infant animals, comprising crushing meat and viscera of fish and shell fish to form a pulp, digesting said pulp with protease (45-50°C); heating the digested pulp to 90-92°C to inactivate the protease, removing the solid matter and suspended particles successively by screening, centrifuging, and filtering the digested pulp to obtain a liquid; defatting the liquid with cyclohexane; condensing the defatted liquid; and reducing the condensed liquid to a powder by spray drying.

D6 - PREV200200413429

Frames without heads from freshly filleted salmon were homogenised and submitted to ProtamexTM hydrolysation. This enzyme was chosen because it is known to produce non-bitter hydrolysates - an important feature as the end product is supposedly usable in human nutrition.
The optimal working conditions of ProtamexTM reported in literature are pH 5.5-7.5 and T=35-60°C.
The authors found in their study that a pH of 6.5-7.6 and a temperature of 50-56°C was optimal for maximum nitrogen (ie protein) recovery.
After enzymatic proteolysis, ProtamexTM was inactivated at 100 +/- 10°C.
Then followed a centrifugation step and the aqueous and oil layers were transferred to a separation funnel. The hydrolysate was collected and filtered.

D7 - PREV200300454780
This article was published online on 7th january 2003. The therein described process for the preparation of a FPH for use in animal nutrition is exactly identical to the one claimed in claims 4-6,12-15 (see pages 4-5 and attached figure 2).

D8 - PREV198988093117 - XP00905809
Fish protein, as well as soy protein, may reduce the risk of atherosclerosis in rabbits, compared to casein.

D9 - PREV199396067465 - XP00905808
The effects of amount and type of dietary fish proteins on plasma and liver cholesterol concentrations were evaluated in female rats.
When compared with casein, cod meat and soya-bean protein decreased plasma and liver cholesterol concentrations. A further cholesterol-lowering effect was achieved by increasing the proportion of either soya-bean protein or cod meal in the diet.

V.4 NOVELTY

Remarks under Art. 33(2) PCT

Document D1 anticipates claims 1-3,8-11,16.
Document D3 anticipates claims 1-3,8-11,16 (compare section III).
Document D7 anticipates claims 1-16 (compare section II for claims 1-3,8-11,16).

Note: Even when assuming a properly formulated second medical use claim, claims 1-3,8-11,16 would still be anticipated by D1 as the "diseases" claimed to be treated in claims 1-3 (fatty liver, hypercholesterolemia, hyperhomocyteinemia) are well-known symptoms of cardiovascular diseases, but not diseases as such.

Claims 1-16 therefore appear to be not novel according to Art. 33(2) PCT.

CLAIMS

1. Use of an enzyme treated fish protein hydrolysate (FPH) material for the preparation of a pharmaceutical or nutritional preparation for the treatment and/or prevention of fatty liver in an animal.

2. Use of the FPH material for the preparation of a pharmaceutical or nutritional composition for the treatment and/or prevention of hypercholesterolemia in an animal.

3. Use of the FPH material for the preparation of a pharmaceutical or nutritional composition for the treatment and/or prevention of hyperhomocysteinemia in an animal.

4. Process for the production of an enzyme treated fish protein hydrolysate (FPH), characterized in that the process comprises the following steps:

a) fish flesh remnants are hydrolyzed with a protease enzyme at a pH in the range of 5,0-8,0, preferable 6,0-7,0, most preferable at about 6,5, and at a temperature in the range of 40 - 70°C, more preferable 50 - 60°C, and most preferable at about 65°C,
b) the temperature is elevated to about 90 – 99 °C
c) an insoluble fraction was removed by decanting and filtering, and the remaining mixture was separated in a three phase separator into an oil fraction, an emulsion fraction and an aqueous fraction, and
d) the aqueous fraction was isolated, and thereafter filtered through a ultramembrane with a nominal molecular weight limit of 100 000, and thereafter spray-dryed.

5. Process in accordance with claim 4, wherein the PFH material contains proteins in the range 70-90%, preferable 80-85%, and most preferable about 83%.

6. Process in accordance with claim 4, wherein the amino acid content of the PFH material is as given in table 2.

7. Use of an enzyme treated fish protein hydrolysate (FPH) material prepared by the process according to claims 4-6 for the preparation of a pharmaceutical or nutritional preparation for the treatment and/or prevention of atherosclerosis, coronary heart disease, stenosis, thrombosis, myocardial infraction and stroke in an animal.

8. Use of the FPH material in accordance with claims 1-3 and 7, wherein said animal is a human.

9. Use of the FPH material in accordance with claims 1-3 and 7, wherein said animal is an agricultural animal, such as gallinaceous birds, bovine, ovine, caprine or porcine mammals.

10. Use of the FPH material in accordance with claims 1-3 and 7, wherein said animal is a domestic or pet animal, such as dog or cat.

11. Use of the FPH material in accordance with claims 1-3 and 7, wherein said animal is a fish or shellfish, such as salmon, cod, Tilapia, clams, oysters, lobster or crabs.

12. Process in accordance with claim 4, wherein the fish material is fish flesh remnants on salmon bone frames after filleting.

13. Process in accordance with claim 4, wherein the hydrolysis is conducted by the enzyme material is a Bacillus protease complex (Protamex™).

14. Process in accordance with claim 4, wherein the enzymatic hydrolysis is performed at a pH in the range of 5,0-8,0, preferable 6,0-7,0, most preferable at about 6,5.

15. Process in accordance with claim 4, wherein the enzymatic hydrolysis is performed at a temperature in the range of 40 - 70°C, more preferable 50 - 60°C, and most preferable at about 65°C.

16. Use in accordance with claims 1-3 and 7-11, wherein the composition is a food grade product or additive, e.g. an animal feed or pet food.